REMARKS

I. Status of the claims

Claims 11, 13-28 and 32 are pending in the application, and stand rejected. Claims 9 (withdrawn), 11, 14, 16-18 and 32 are amended herewith, and claim 15 is canceled herein without prejudice. New claim 33 has been added.

II. Amendments to the claims

Withdrawn claim 9 had been amended to correct a typographical error. Claim 11 has been amended to replace the term "hydrophobic matrix carrying system" with "lipid complex forming lipids selected from the group consisting of phosphatidylcholines, sterols, and combinations thereof." Support for this amendment can be found, for example, at page 6-7 of the specification, which describes various lipids that may be used in the present method. Claim 14 had been amended to correct a typographical error. Claims 16-18 have been amended to correct claim dependencies. Claim 32 has been amended to more distinctly claim what Applicants regard as the invention by deleting the words "liposomes or" from the claim . Support for these amendments can be found, for example, in the claims and the specification as originally filed, such as at pages 7-8 of the specification. New claim 33 recites that the temperature differential is 15 °C or more. Support for this new claim can be found in the specification, for example, at paragraph 20, which describes various temperature ranges for the heating and cooling steps. No new matter has been added.

III. Rejections under 35 U.S.C. § 103

A. Abra in view of Ye

The Examiner has rejected claims 12, 16, 19-23 as being obvious over Abra in view of U.S. Patent No. 5,998,899 to Ye et al. ("Ye"). The Examiner notes that "[w]hat is lacking in Abra is the

repetition of the heating and cooling." *Office Action* at p. 2. The Examiner further notes that Abra does not teach the use of DPPC. *Id.* According to the Examiner, it would have been obvious "[t]o employ three cooling and heating cycles in the method . . . of Abra . . . since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes." *Office Action* at p. 3. Furthermore, the Examiner asserts that it would have been obvious to use DPPC instead of HSPC taught by Abra. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Fed. Reg. Vol. 72, No. 195 at p. 57528.

Abra teaches liposome compositions containing lipids derivatized with a hydrophilic polymer (e.g., PEG) for improved liposome stability. Ye describes a method for preparing multivesicular liposomal formulations having increased encapsulation efficiency by increasing the number of carbons in the carbon chain at least one of the amphipathic lipids. *Ye* at col. 2, ll. 8-18.

Applicants submit that the Examiner has not provided "some articulated reasoning with some rational underpinning" for the skilled artisan to employ the temperature cycling of Ye in the process of Abra. In particular, there is no reason for the skilled artisan to employ Ye's temperature cycling, which was used with PC's having 14-20 carbons, in a formulation comprising the hydrophilic polymer modified liposomes of Abra, which are modified with, for example, PEG chains of 500-10,000 Daltons, with any reasonable expectation of success. Nothing in the teachings of Ye suggest that temperature cycling would be facilitate drug equilibrium in a liposome comprising the hydrophilic polymer derived vesicles of Abra.

Additionally, Ye only discloses the use of temperature cycling in a single example (Example 5) of the disclosure, which describes the preparation of multilamellar liposomes encapsulating cytarabine. As cytarabine is a small organic molecule, not a platinum compound, there is no reason the skilled artisan would readily conclude that platinum compounds would behave similarly to cytarabine and combine the teachings of Ye with Abra.

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

B. Yamauchi in view of Abra and Ye

The Examiner has rejected claims 11-28 and 32 as being obvious over U.S. Publication 2002/0182248 to Yamauchi ("Yamauchi"). The Examiner acknowledges that Yamauchi does not teach " the use of cisplatin as the drug and also repeating the steps of changing the temperature in two or more cycles." *Office Action* at p. 4. The Examiner contends that it would have been obvious to use cisplatin in the method of Yamauchi "since Yamauchi teaches that any drug can be encapsulated and . . . Abra shows the knowledge in the art of encapsulating cisplatin." *Id.* at p. 5 The Examiner further contends that it would have been obvious "[t]o employ three cooling and

heating cycles . . . since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes." *Id.* at p. 5. Applicants respectfully traverse.

Yamauchi describes "liposomes and liposomal dispersions in which stability of drugs which have poor stability in the aqueous solution is improved." *Yamauchi* at ¶ 7. In particular, Yamauchi states that the stability of the aforementioned drugs becomes "markedly excellent when they are incorporated in liposomes prepared using a specified lipid," where the sphingolipid is "the main component of the liposomal membrane." *Id.* at ¶ 8-9.

In contrast, the process of Applicants' claims do not include sphingolipids. Thus, the Applicants submit that the Examiner has not provided any "articulated reasoning with some rational underpinning" for the skilled artisan to use cisplatin in the sphingolipid liposomes of Yamauchi. Abra teaches encapsulation of cisplatin in liposomes comprising lipids specifically derivatized with hydrophilic polymer chains. The hydrophilic chains, according to Abra improve stability of the cisplatin and blood circulation. Abra's teachings provide no reasonable expectation of success for efficiently encapsulating cisplatin in the liposomes of Yamauchi. For at least this reason, the above reference combination fails to render the instant claims obvious.

Ye, which the examiner relies for disclosing three cycles of heating cooling, fails to remedy the deficiencies of Abra and Yamauchi. Specifically, Ye provides no teaching of encapsulating cisplatin. Additionally, nothing in Ye would provide any reasonable expectation of success in using the temperature cycling disclosed in Ye, which was applied to saturated and unsaturated PC's, to the sphingolipids of Yamauchi. For at least these reasons, Applicants respectfully request withdrawal of this rejection.

Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-006.01.**

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